This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1 - 61. (Canceled)

62. (Previously presented) A method for producing hybridoma cells producing antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells;

(d) removing said chemical inhibitor of mismatch repair from said hypermutated hybridoma cells, thereby stabilizing the genome of said hypermutated hybridoma cells,

(e) screening antibodies produced from said hypermutated hybridoma cells for binding to antigen; and

(f) selecting hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells;

thereby producing hybridoma cells producing antibodies having higher affinity for said antigen than antibodies produced by said parental hybridoma cells.

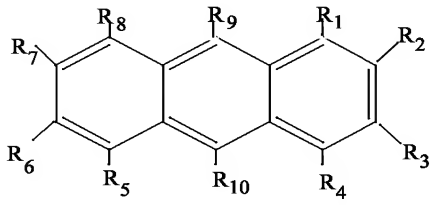
63. (Previously presented) The method of claim 62 wherein said chemical inhibitor of mismatch repair is an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor, or an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

64. (Previously presented) A method for producing hybridoma cells producing antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells, wherein said chemical inhibitor of mismatch repair is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups;

(d) screening antibodies produced from said hypermutated hybridoma cells for binding to antigen; and

(e) selecting hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells;

thereby producing hybridoma cells producing antibodies having higher affinity for said antigen than antibodies produced by said parental hybridoma cells.

65. (Original) The method of claim 64 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

66. (Previously presented) The method of claim 62 further comprising screening for hypermutated hybridoma cells that also produce antibodies in higher titers than said parental hybridoma cells.

67. (Canceled)

68. (Previously presented) The method of claim 64 further comprising the step of removing said chemical inhibitor of mismatch repair from said hypermutated hybridoma cells, thereby stabilizing the genome of said hypermutated hybridoma cells.

69. (Previously presented) The method of claim 62 wherein said antibodies having higher affinity for said antigen than antibodies produced by said parental hybridoma cells have an affinity for said antigen of at least about 1×10^7 M^{-1} to about 1×10^{14} M^{-1}.

70. (Previously presented) The method of claim 66 wherein said hypermutated hybridoma cells that produce antibodies in higher titers than said parental hybridoma cells have a titer that is at least about 1.5-8 fold greater than the titer produced by said parental hybridoma cells.

71-72. (Canceled)

73. (Previously presented) A method for producing hybridoma cells that produce antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells;

(d) removing said chemical inhibitor of mismatch repair from said hypermutated hybridoma cells, thereby stabilizing the genome of said hypermutated hybridoma cells; and

(e) selecting hypermutated hybridoma cells that produce higher titers of antigen-specific antibodies than said parental hybridoma cells;

thereby producing hybridoma cells that produce higher titers of antibodies than said parental hybridoma cells.

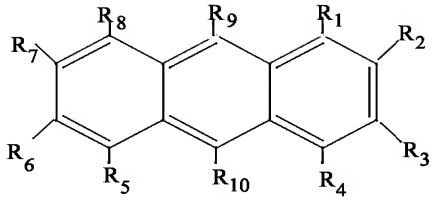
74. (Previously presented) The method of claim 73 wherein said chemical inhibitor of mismatch repair is an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor, or an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

75. (Previously presented) A method for producing hybridoma cells that produce antibodies from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells, wherein said chemical inhibitor of mismatch repair is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups; and

(d) selecting hypermutated hybridoma cells that produce higher titers of antigen-specific antibodies than said parental hybridoma cells;

thereby producing hybridoma cells that produce higher titers of antibodies than said parental hybridoma cells.

76. (Original) The method of claim 75 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

77. (Previously presented) The method of claim 75 further comprising the step of removing said chemical inhibitor of mismatch repair from said hypermutated hybridoma cells, thereby stabilizing the genome of said hypermutated hybridoma cells.

78. (Previously presented) The method of claim 73 wherein said higher titer of said antibodies is a titer of at least about 1.5-8 fold greater than the titer of said parental hybridoma cells.

79-80. (Canceled)

81. (Previously presented) A method for producing mammalian expression cells that produce antibodies comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells;

(c) performing a screen for binding of antibodies produced from said hybridoma cells to antigen;

(d) cloning immunoglobulin genes from hybridoma cells that produce antibodies to said antigen into a mammalian expression cell;

(e) incubating said mammalian expression cell in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated mammalian expression cells;

(f) removing said chemical inhibitor of mismatch repair from said hypermutated mammalian expression cells, thereby stabilizing the genome of said hypermutated mammalian expression cells; and

(g) performing a screen for hypermutated mammalian expression cells that secrete antibodies with higher affinity for antigen as compared to antibodies produced from said hybridoma cells that produce antibodies to said antigen;

thereby producing mammalian expression cells that produce antibodies having higher affinity for said antigen than said hybridoma cells that produce antibodies to said antigen.

82. (Previously presented) The method of claim 81 wherein said chemical inhibitor of mismatch repair is an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA interference molecule, a polymerase inhibitor, or an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

83. (Previously presented) A method for producing mammalian expression cells that produce antibodies comprising:

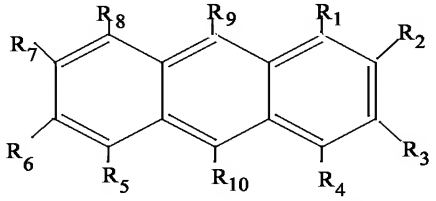
(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form hybridoma cells;

(c) performing a screen for binding of antibodies produced from said hybridoma cells to antigen;

(d) cloning immunoglobulin genes from hybridoma cells that produce antibodies to said antigen into a mammalian expression cell;

(e) incubating said mammalian expression cell in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated mammalian expression cells, wherein said chemical inhibitor of mismatch repair is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups; and

(f) performing a screen for hypermutated mammalian expression cells that secrete antibodies with higher affinity for antigen as compared to antibodies produced from said hybridoma cells that produce antibodies to said antigen;

thereby producing mammalian expression cells that produce antibodies having higher affinity for said antigen than said hybridoma cells that produce antibodies to said antigen.

84. (Original) The method of claim 83 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

85. (Previously presented) The method of claim 81 further comprising performing a screen for hypermutated mammalian expression cells that also produce antibodies in higher titers than said hybridoma cells that produce antibodies to said antigen.

86. (Previously presented) The method of claim 81 wherein said antibodies having higher affinity for said antigen than said hybridoma cells that produce antibodies to said antigen have an affinity for said antigen of at least about $1 \times 10^7\ M^{-1}$ to about $1 \times 10^{14}\ M^{-1}$.

87. (Previously presented) The method of claim 85 wherein said higher titers of said antibodies is at least about 1.5-8 fold greater that the titer produced by said hybridoma cells that produce antibodies to said antigen.

88. (Previously presented) The method of claim 83 further comprising removing said chemical inhibitor of mismatch repair from said hypermutated mammalian expression cells, thereby stabilizing the genome of said hypermutated mammalian expression cells.

89 - 90. (Canceled)

91. (Previously presented) A method for producing mammalian expression cells that produce antibodies to a selected antigen from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair to form hypermutated hybridoma cells;

(d) removing said chemical inhibitor of mismatch repair from said hypermutated hybridoma cells, thereby stabilizing the genome of said hypermutated hybridoma cells;

(e) performing a screen for binding of antigen for antibodies produced from said hypermutated hybridoma cells;

(f) selecting hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells;

(g) cloning immunoglobulin genes from said hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells into a mammalian expression cell, thereby forming parental mammalian expression cells;

thereby producing mammalian expression cells that produce antibodies having higher affinity for said antigen than said parental hybridoma cells from *in vitro* immunized immunoglobulin-producing cells.

92. (Previously presented) The method of claim 91 wherein said chemical inhibitor of mismatch repair is an anthracene, ATPase inhibitor, a nuclease inhibitor, an RNA

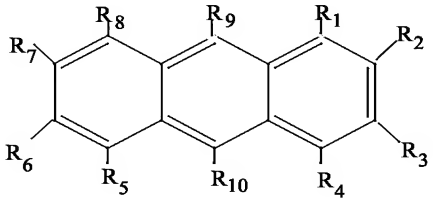
interference molecule, a polymerase inhibitor, or an antisense oligonucleotide that specifically hybridizes to a nucleotide encoding a mismatch repair protein.

93. (Previously presented) A method for producing mammalian expression cells that produce antibodies to a selected antigen from *in vitro* immunized immunoglobulin-producing cells comprising:

(a) combining donor cells comprising immunoglobulin-producing cells with an immunogenic antigen *in vitro*;

(b) fusing said immunoglobulin-producing cells with myeloma cells to form parental hybridoma cells;

(c) incubating said parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair to form hypermutated hybridoma cells, wherein said chemical inhibitor of mismatch repair is an anthracene having the formula:



wherein R_1-R_{10} are independently hydrogen, hydroxyl, amino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, O-alkynyl, S-alkynyl, N-alkynyl, aryl, substituted aryl, aryloxy, substituted aryloxy, heteroaryl, substituted heteroaryl, aralkyloxy, arylalkyl, alkylaryl, alkylaryloxy, arylsulfonyl, alkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, guanidino, carboxy, an alcohol, an amino acid, sulfonate, alkyl sulfonate, CN, NO_2, an aldehyde group, an ester, an ether, a crown ether, a ketone, an organosulfur compound, an organometallic group, a carboxylic acid, an organosilicon or a carbohydrate that optionally contains one or more alkylated hydroxyl groups;

wherein said heteroalkyl, heteroaryl, and substituted heteroaryl contain at least one heteroatom that is oxygen, sulfur, a metal atom, phosphorus, silicon or nitrogen; and wherein said substituents of said substituted alkyl, substituted alkenyl, substituted alkynyl, substituted

aryl, and substituted heteroaryl are halogen, CN, NO_2, lower alkyl, aryl, heteroaryl, aralkyl, aralkoxy, guanidino, alkoxycarbonyl, alkoxy, hydroxy, carboxy and amino; and

wherein said amino groups are optionally substituted with an acyl group, or 1 to 3 aryl or lower alkyl groups;

(d) performing a screen for binding of antigen for antibodies produced from said hypermutated hybridoma cells;

(e) selecting hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells; and

(f) cloning immunoglobulin genes from said hypermutated hybridoma cells that produce antibodies with higher affinity for said antigen than antibodies produced by said parental hybridoma cells into a mammalian expression cell, thereby forming parental mammalian expression cells;

thereby producing mammalian expression cells that produce antibodies having higher affinity for said antigen than said parental hybridoma cells from *in vitro* immunized immunoglobulin-producing cells.

94. (Previously presented) The method of claim 93 wherein R_1-R_{10} are independently hydrogen, hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl, tolyl, hydroxymethyl, hydroxypropyl, or hydroxybutyl.

95. (Previously presented) The method of claim 91 wherein said antibodies having higher affinity for said antigen than said parental hybridoma cells have an affinity for said antigen of at least about $1 \times 10^7\ M^{-1}$ to about $1 \times 10^{14}\ M^{-1}$.

96. (Previously presented) The method of claim 91 further comprising the steps of:

incubating said parental mammalian expression cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated mammalian expression cells; and

screening for hypermutated mammalian expression cells that produce a higher titer of antibodies than said parental mammalian expression cells.

97. (Previously presented) The method of claim 93 further comprising removing said chemical inhibitor of mismatch repair from said hypermutated hybridoma cells, thereby stabilizing the genome of said hypermutated hybridoma cells.

98. (Previously presented) The method of claim 96 further comprising removing said chemical inhibitor of mismatch repair from said hypermutated mammalian expression cells, thereby stabilizing the genome of said hypermutated mammalian expression cells.

99. (Previously presented) The method of claim 96 wherein said higher titer of antibodies is at least about 1.5-8 fold greater than the titer produced by said parental mammalian expression cells.

100-134. (Canceled)

135. (Original) The method of claim 62, 73, 81, 91, 117, or 127 wherein said chemical inhibitor of mismatch repair is an antisense molecule comprising at least 15 consecutive nucleotides of a sequence encoding a protein selected from the group consisting of SEQ ID NO:2; SEQ ID NO:4; SEQ ID NO:6; SEQ ID NO:8; SEQ ID NO:10; SEQ ID NO:12; SEQ ID NO:14; SEQ ID NO:16; SEQ ID NO:18; SEQ ID NO:20; SEQ ID NO:22; SEQ ID NO:24; SEQ ID NO:26; SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:32; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:38; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:44; SEQ ID NO:46; SEQ ID NO:48; and SEQ ID NO:50.

136. (Original) The method of claim 62, 73, 81, 91, 117, or 127 wherein said chemical inhibitor of mismatch repair is an antisense molecule comprising at least 15 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13; SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; SEQ ID NO:21; SEQ ID NO:23; SEQ ID NO:25; SEQ ID NO:27; SEQ ID NO:29; SEQ ID NO:31; SEQ ID NO:33; SEQ ID

NO:35; SEQ ID NO:37; SEQ ID NO:39; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:45; SEQ ID NO:47; and SEQ ID NO:49.

137-138. (Canceled)

139. (Previously presented) The method of claim 93 wherein said antibodies having higher affinity for said antigen than said parental hybridoma cells have an affinity for said antigen of at least about 1 x 10^7 M^{-1} to about 1 x 10^{14} M^{-1}.

140. (Previously presented) The method of claim 93 further comprising the steps of:

incubating said parental mammalian expression cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated mammalian expression cells; and

screening for hypermutated mammalian expression cells that produce a higher titer of antibodies than said parental mammalian expression cells.

141. (Previously presented) The method of claim 140 further comprising removing said chemical inhibitor of mismatch repair from said hypermutated mammalian expression cells, thereby stabilizing the genome of said hypermutated mammalian expression cells.

142. (Previously presented) The method of claim 140 wherein said higher titer of antibodies is at least about 1.5-8 fold greater than the titer produced by said parental mammalian expression cells.

143. (Previously presented) The method of claim 83 further comprising performing a screen for hypermutated mammalian expression cells that also produce antibodies in higher titers than said hybridoma cells that produce antibodies to said antigen.

144. (Previously presented) The method of claim 83 wherein said antibodies having higher affinity for said antigen than said hybridoma cells that produce antibodies to said antigen have an affinity for said antigen of at least about 1 x 10^7 M^{-1} to about 1 x 10^{14} M^{-1}.

145. (Previously presented) The method of claim 143 wherein said higher titers of said antibodies is at least about 1.5-8 fold greater that the titer produced by said hybridoma cells that produce antibodies to said antigen.

146. (Previously presented) The method of claim 75 wherein said higher titer of said antibodies is a titer of at least about 1.5-8 fold greater than the titer of said parental hybridoma cells.

147. (Previously presented) The method of claim 64 further comprising screening for hypermutated hybridoma cells that also produce antibodies in higher titers than said parental hybridoma cells.

148. (Previously presented) The method of claim 147 further comprising removing said chemical inhibitor of mismatch repair from said hypermutated hybridoma cells, thereby stabilizing the genome of said hypermutated hybridoma cells.

149. (Previously presented) The method of claim 64 wherein said antibodies having higher affinity for said antigen than antibodies produced by said parental hybridoma cells have an affinity for said antigen of at least about $1 \times 10^{7}\ M^{-1}$ to about $1 \times 10^{14}\ M^{-1}$.

150. (Previously presented) The method of claim 147 wherein said hypermutated hybridoma cells that produce antibodies in higher titers than said parental hybridoma cells have a titer that is at least about 1.5-8 fold greater than the titer produced by said parental hybridoma cells.